Remarks

Claims 1, 14-17, 20-27, 30-33, 63, and 64 are pending after entry of this Amendment. Claims 2-13, 18, 19, 28, 29, and 34-62 have been canceled in this Amendment or previously. Claims 1 and 14 are amended herein. Claims 63 and 64 have been added. Claim 1 is the only independent claim pending.

No fee for additional claims is believed due, since more than two claims were canceled and only two dependent claims were added.

No new matter is added by the amendments and additions made herein.

The amendments to claim 1 incorporate the recitations of now-canceled claim 8. The Applicants have also amended claim 1 to explicitly recite that the claims encompass only assessment of "known" disorder-associated polymorphisms. This amendment is supported in the specification, for example at paragraph **[0026]**, in which paragraph the term 'disorder-associated' polymorphism is defined to mean a form of a gene (or a portion of a gene) that has been correlated with exhibition of a disease or pathological state. Therefore, this amendment does not include new matter, since it merely makes explicit in the claims that which is stated in the specification.

The amendment to claim 14 merely substitutes the abbreviation "DAP" in place of the longer term "disorder-associated polymorphism." This abbreviation is indicated in claim 1.

New claims 63 and 64 merely recite the polymorphisms recited in originally-filed claim 33. Claims 63 and 64 are believed to correspond to the elected Group and species, in that each of these claims recites vitamin D receptor genes and interleukin-6 genes. Examination of claims 63 and 64 together with the remaining claims is believed to be appropriate.

The rejections made in the Office Action are now addressed in the order in which they appeared in the Office Action.

Rejection Pursuant to 35 U.S.C. § 112, First Paragraph -- Written Description

In the rejection spanning pages 2-5 of the Office Action, the Examiner rejects all of the pending claims pursuant to the written description requirement of 35 U.S.C. § 112, first paragraph. In the Examiner's view, the claims recite using an essentially unlimited number of disorder-associated polymorphisms - including many which have not yet been discovered. The Examiner believes that recitation of assessing occurrence of as-yet-undiscovered polymorphisms fails to satisfy the statutory written description requirement.

As is made explicit in the claims as amended, the "known disorder-associated polymorphisms" are not simply any polymorphic genetic form that is associated with a disease or pathological state (i.e., whether such association is known or unknown). To the contrary, the specification explicitly teaches (see paragraphs **[0021]**, **[0026]**, and **[0036-0038]**, for example) that the relevant polymorphisms are those that are known to be associated with a disorder in one of the specified genes. In effect, the applicants have discovered that if a polymorphism occurs in one of those genes and causes sufficient dysfunction that its occurrence is associated with a disorder (i.e., ANY disorder - not necessarily a bone density disorder), then the bone density of the person harboring the disorder-associated polymorphism will be adversely affected. The precise identity of the polymorphism and the disorder associated with it are immaterial - it is the fact that the association between the polymorphism and the disorder exists that is material to the claimed method.

The Examiner correctly understands that the specification discloses numerous disorder-associated polymorphisms in the genes recited in the claims, and that other disorder-associated polymorphisms in those genes (i.e., polymorphisms not listed in the specification) will likely be discovered in the future. However, the Examiner believes that knowledge of the identity of those yet-to-be-discovered polymorphisms is required for possession by the inventors of the claimed invention. With all due respect, the Applicants believe that the Examiner is wrong on this point.

It is well within the level of skill of an ordinary worker in this field to perform a search of all polymorphisms that are associated with any particular gene and to identify those which have

been associated with a disease or other pathological condition. By way of example, such searches can be routinely performed using the NCBI's Single Nucleotide Polymorphism database (dbSNP, available at http://www.ncbi.nlm.nih.gov/SNP/) or the Online Mendelian Inheritance in Man (OMIM; TM, Johns Hopkins University) database of McKusick et al. (available, for example, at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

The Applicants respectfully contend that the Examiner is mischaracterizing the Applicants' invention as merely a collection of specific polymorphisms that can be correlated with bone density of a patient. Instead, the Applicants have invented a generic method of assessing occurrence of a certain type of polymorphisms that can be used to assess bone density conditions.

Analogously, one who claims a certain combination of mechanical parts held together by "nails" should not be limited to claims only to the particular types of nails disclosed in the specification or the particular types of nails available on the date the corresponding application was filed. So long as any type of "nail" will fulfill the required purpose, the claim should encompass both existing and later-developed nails. Here, the Applicants have identified a class of polymorphisms that are useful for assessing bone density conditions. The characteristics of all of the polymorphisms in that class are i) that they occur in one of the genes recited in claim 1; and ii) that they have a known association with a disorder of any type. The Applicants respectfully contend that a skilled artisan understands that this class of polymorphisms (like the class of "nails") includes both polymorphisms that are currently known and others for which the association between the polymorphism and a disorder will become known later (just as particular alloys, shapes, and colors of "nails" can be developed beyond the types already known.)

The Examiner's concentration on the nucleotide sequences of polymorphisms other than those listed in claim 1 (and in claim 64) is believed to be misplaced because the Applicants are not claiming the sequences themselves. Those sequences are simply information that is available in the art to skilled artisans (i.e., the recited polymorphisms are all polymorphisms having a

"known" association with a disorder), and the specification need not provide information that is available in the art to skilled artisans.

For the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the rejection of all of the claims pursuant to the written description of the first paragraph of 35 U.S.C. §112.

Rejection Pursuant to 35 U.S.C. § 112, First Paragraph -- Enablement

In the rejection spanning pages 5-9 of the Office Action, the Examiner rejects all of the pending claims pursuant to the enablement requirement of 35 U.S.C. § 112, first paragraph. In the Examiner's view, the claims recite subject matter that was not described adequately enough that a skilled artisan could make and use the invention. The Examiner evidently believes that the invention cannot be practiced without knowing the identity of every possible disorder-associated polymorphism (DAP).

As explained in the foregoing section relating to the Examiner's written description rejection, the claims have been amended to explicitly recite assessment of known DAPs. Furthermore, 15 such DAPs are explicitly disclosed in the specification. A skilled artisan is able to select DAPs from the 15 disclosed or to search the literature to readily identify other known DAPs. The claims do not extend beyond known DAPs. The technical skill required to assess occurrence of multiple DAPs is trivial at most. The Applicants respectfully contend that a skilled artisan in this field would have no difficulty selecting two or more DAPs for the genes recited in the claims or in assessing their occurrence in an individual. The Examiner is requested to reconsider and withdraw the rejection of all of the pending claims pursuant to the enablement requirement of the first paragraph of 35 U.S.C. § 112.

The Examiner faults the specification for not providing an explicit, statistically significant, link between occurrence of a DAP in one of the genes recited and an undesirable bone density condition. The Applicants believe this emphasis to be misplaced. The claims do not recite a method of diagnosing existence of such a condition, but rather a way of assessing

relative susceptibility to such conditions -- that is, the claims recite a method of providing an indication (not a definitive diagnosis) of the relative likelihood that a human will develop such a condition.

In the context of an enablement rejection premised on purported inoperability of the claimed invention, the Examiner should properly examine whether a skilled artisan in this field would, more likely than not, believe that the claimed invention could be used for its intended purpose. The Applicants believe that the Examiner has improperly considered that intended purpose to be definitive diagnosis of a bone density condition, rather than the purpose recited in the claim -- to "assess[] relative susceptibility of a human to an undesirable bone density condition." In the context of this recited purpose and the following explanation, the Applicants respectfully contend that a skilled artisan in this field would find it credible that the claimed invention could be used for its intended purpose.

The specification discloses that association between occurrence of a polymorphism and manifestation of a disease is not merely a link between the polymorphism and the disease (i.e., per the old one-polymorphism/one-disease paradigm), but that this association is also an indication that the polymorphism is associated with a loss of physiological function of the product of the corresponding gene (see specification paragraph **[0045]** for example). The Applicants recognized that if that loss of physiological function was significant enough to cause or contribute to the polymorphism-associated disease, then the loss of function was indicative that other physiological processes in which the gene product is involved would also be adversely affected. Put another way, the Applicants realized that if the product of the (presumably fictitious) *xyz* gene is sufficiently faulty that it causes or contributes to Disease 1, then the *xyz* gene product is faulty (or at least sub-optimal) for all or substantially all processes in which the *xyz* gene product has a physiological role.

The Applicants believe that they are the first to recognize that the susceptibility of an individual for undesirable bone density conditions can be assessed by looking at the cumulative effects of disorder-associated polymorphisms in genes whose products have important roles in

bone density (e.g., in two or more of the genes disclosed in the specification). The Applicants also believe that they were the first to recognize that it makes no difference to which disease state a polymorphism in a relevant gene is associated -- association of a polymorphism in a gene affecting bone density with any disease or disorder is an indicator of lesser gene product function and hence of greater susceptibility to undesirable bone density conditions.

Thus, the Applicants derived their new paradigm: that an assessment of a somewhat-complicated physiological system such as human bone density can be made by looking at signs of dysfunction in the gene products that contribute to the overall health of the system -- and that such dysfunction is manifested by occurrence of polymorphisms (in those genes and gene products) that are associated with a disease state in the same or an entirely different physiological system.

In order establish non-enablement on the grounds of inoperability, the Examiner must provide a credible, art-supported reason why a skilled artisan in this field would not find the Applicants' assertions of operability to be credible. At most, the Examiner has suggested that the claimed methods cannot be linked with definitive diagnosis of undesirable bone density conditions. However, the claims do not recite definitive diagnosis. The Applicants respectfully suggest that a skilled artisan in this field would understand, in view of the explanations provided in the specification (and in this Amendment), that the claimed methods can be used to assess relative susceptibility to such conditions.

Reconsideration and withdrawal of the Examiner's rejection of the claims in view of the enablement requirement of 35 U.S.C. § 112, first paragraph, are respectfully requested.

Summary

The Applicant believe that each of claims 1, 14-17, 20-27, 30-33, 63, and 64 is in condition for allowance. Issuance of a Notice of Allowance is respectfully requested at the earliest possible time.

Respectfully submitted,

JOHN R. DEPHILLIPO ET AL.

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(Date)

GARY D. COLBY, Ph.D., J.D.
Registration No. 40,961
Customer No. 08933
DUANE MORRIS LLP
30 South 17th Street
Philadelphia, PA 19103-4196
Telephone: 215-979-1000
Direct Dial: 215-979-1849
Facsimile: 215-979-1020
E-Mail: GDColby@DuaneMorris.com

PH1\1520630.1